Remarks

Claims 1-25 and 32-37 are pending in the subject application. By this Amendment, Applicant has canceled claims 16 and 24, amended claims 1, 12-14, 17, 21, 22, 32 and 33 and added new claims 38-44. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, original claims 16 and 24 and page 36 of the as-filed application). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-15, 17-25 and 32-44 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

The Office Action indicates that drawings are objected to because the text, including axis labels, of Figures 1-5 and 10-12 is small and difficult to read. By this Amendment, Applicant has replaced all the drawings to increase the font size of the text. No new matter has been added by these amendments. Entry and review of the replacement drawings is respectfully requested. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

The specification is objected to because it contained embedded hyperlinks or other forms of browser executable code. Applicant respectfully submits that this issue is moot in view of the amendments made to the specification. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 1 and 12-14 are objected to because of informalities. Applicant gratefully acknowledges the Examiner's careful review of the subject specification. In accordance with the Examiner's suggestions, Applicant has inserted the acronym for 2-methylpropyl-beta-cycldextrin ("HPBCD") in parenthesis and replaced "said the antioxidant" with "said antioxidant." Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 33 is objected to under 37 C.F.R. 1.75(c) as being of improper dependent form. The Office Action indicates that "the article of manufacture that is a container for administration would necessarily be for either mono- or multi-dose (i.e. one or more than one) administration because these would be the only possibilities." By way of this amendment, claim 33 and been amended and new claim 38 added to individually recite either a mono-dose container or a multi-dose container. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 1-25 and 32-37 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action states that the specification has not described the claimed genus of IFN muteins, functional derivatives, and active fragments in such a way as to convey to a person of ordinary skill in the art that the Applicant had possession of the claimed genus at the time of the invention. Applicant respectfully asserts that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention; however, by way of the amendments made in this response, it is respectfully submitted that this issue is now moot. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 21 and 22 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite, because there is insufficient antecedent basis for the limitation "said bacteriostatic" agent. By way of this amendment by correcting the dependencies of these claims, Applicant respectfully asserts that the claims are now definite. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 1-11, 13-19, 21, 22 and 25 are rejected under 35 U.S.C. § 103(a) as obvious over Shirley *et al.* (U.S. Published Patent Application No. 2002/0172661) in view of Dorin *et al.* (U.S. Patent No. 5,814,485). The Office Action indicates that Shirley *et al.* teach stabilized liquid formulations of IFN-β, including recombinant IFN-β in a solution with a buffer, wherein the buffer is in an amount sufficient to maintain the pH of the composition within plus or minus 0.5 units of a specified pH, wherein the specified pH is about 3.0 to about 5.0, and wherein the IFN-β concentration can range from 0.01 mg/ml to 20 mg/ml (10 μg/ml - 20,000 μg/ml). The Office Action also indicates that Shirley *et al.* teach numerous suitable buffers, including acetate buffer at a concentration range of 1 - 30 mM and that this composition can further comprise a "tonicifying agent" such as mannitol. Finally, Shirley *et al.* is cited as teaching inclusion of bacteriostatic agents. The Office Action alleges that Dorin *et al.* teach compositions comprising IFN-β, and teach that these IFN-β formulations can comprise 2-hydroxypropyl-beta-cyclodextrin, and also teach that inclusion of 2-hydroxypropyl-beta-cyclodextrin is useful as a protectant because it helps reduce the

physical and chemical alterations to IFN-β polypeptides, such as oxidation. The Office Action also asserts that the Dorin *et al.* patent teaches that 2-hydroxypropyl-beta-cyclodextrin helps prevent unwanted aggregation, chemical linkage, oxidation, and degradation of IFN-β. Applicant further notes that the Office Action asserts (at page 7) that "it is noted that a person of ordinary skill in the art would have the motivation, and the ability, to optimize the concentrations or amounts of various reagents in order to create the most effectively stabilized formulation. M.P.E.P 2144.05 states: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 U.S.P.Q. 223, 235, (C.C.P.A. 1955)." Applicant respectfully asserts that the claimed invention is not obvious over the cited references and traverses the rejection.

While Applicant notes that the Office Action cites to M.P.E.P §2144.05 for support for the proposition that "a person of ordinary skill in the art would have the motivation, and the ability, to optimize the concentrations or amounts of various reagents in order to create the most effectively stabilized formulation" it is also noted that the Office Action does not reference M.P.E.P §2144.05(II)(B) where it is stated:

> **B. Only Result-Effective Variables Can Be Optimized**
>
> A particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (C.C.P.A. 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.).

In this case, the Office Action has failed to establish that the concentration of 2-hydroxypropyl-beta-cyclodextrin was "recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result". Applicant further notes that the Office Action has also failed to establish that mannitol, EDTA, acetate buffer and/or bacteriostatic agents were art recognized result-effective variables. Thus, it is respectfully submitted that a *prima facie* case of obviousness has not been established by the cited combination of references.

Even assuming, *arguendo*, that the Patent Office is able to establish that the concentrations of these components within the claimed composition are recognized as a result effective variables, it is respectfully submitted that the combination of Shirley *et al.* and Dorin *et al.* fail to teach each and every element of the claimed invention. For example, the combination of Shirley *et al.* and Dorin *et al.* fail to teach limitations such as those found in previously pending claim 16 (drawn to a composition in which HPBCD is present at about a 500-fold to about a 700-fold molar excess with respect to interferon). As the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention (*CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)). Additionally, Applicant further submits that there is no motivation to add a second anti-oxidant (*i.e.*, HPBCD) to the composition of Shirley *et al.* and the Office Action provides no articulated reasoning as to why one skilled in the art would have been so motivated.

Additional guidance regarding obviousness determinations has been provided by the Court of Appeals for the Federal Circuit in *Bayer Schering Pharma AG. v. Barr Lab., Inc.*, 575 F.3d 1341, 1347, 91 USPQ2d 1565, 72-73 (Fed. Cir. 2009). There it is stated:

> In *KSR*, the Supreme Court stated that an invention may be found obvious if it would have been obvious to a person having ordinary skill to try a course of conduct:
>
> > When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.
>
> 550 U.S. at 421, 127 S.Ct. 1727. This approach is consistent with our methodology in *In re O'Farrell*, 853 F.2d 894 (Fed.Cir.1988). *See Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 996-97 (Fed.Cir.2009); *In re Kubin*, 561 F.3d 1351, 1359, (Fed.Cir.2009). *O'Farrell* observed that most inventions that are obvious were also obvious to try, but found two classes where that rule of thumb did not obtain.
>
> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior

> art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell,* 853 F.2d at 903. This is another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble,* 566 F.3d at 996; *Kubin,* 561 F.3d at 1359. It is also consistent with our interpretation that KSR requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.,* 520 F.3d 1358, 1364 (Fed.Cir.2008).
>
> Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell,* 853 F.2d at 903. This expresses the same idea as the *KSR* requirement that the identified solutions be "predictable." 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble,* 566 F.3d at 996-97; *Kubin,* 561 F.3d at 1359-60.

In this case, Applicant submits that both this application (see page 3, lines 18-24) and Shirley *et al.* (at paragraph 6) indicate:

> The stabilization of polypeptides in pharmaceutical compositions remains an area in which trial and error plays a major role (reviewed by *Wang (1999) Int. J. Pharm. 185:129-188; Wang and Hanson (1988) J. Parenteral Sci. Tech. 42:S3-S26*). Excipients that are added to polypeptide pharmaceutical formulations to increase their stability include buffers, sugars, surfactants, amino acids, polyethylene glycols, and polymers, but the stabilizing effects of these chemical additives vary depending on the protein.

Applicant further notes that neither Shirley *et al.* or Dorin *et al.* "guide an inventor toward a particular solution" and that the references, at best, provide only general guidance to the claimed invention. Thus, it is respectfully submitted that a *prima facie* case of obviousness has not been established and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 12, 20, 23, 24, 32-35 and 37 are rejected under 35 U.S.C. § 103(a) as obvious over Shirley *et al.* (U.S. Published Patent Application No. 2002/0172661) in view of Dorin *et al.* (U.S.

Patent No. 5,814,485) further in view of Chen *et al.* (U.S. Patent No. 6,569,420). The Office Action indicates that Shirley *et al.* further teach stabilized liquid IFN-β formulations in sealed vials suitable for unit-dose or multi-dose and specifically teach liquid formulations in pre-filled syringes for single-dose or multi-dose administration. The Office Action also notes that neither Shirley *et al.* or Dorin *et al.* specifically teach a stabilized composition comprising IFN-β that contains methionine and/or benzyl alcohol. In an effort to remedy these deficiencies in the teachings of Shirley *et al.* and Dorin *et al.*, the Office Action argues that Chen *et al.* teach that IFN compositions can be formulated using both methionine and benzyl alcohol. Applicant respectfully asserts that the claimed invention is not obvious over the cited references.

As noted above, the combination of Shirley *et al.* and Dorin *et al.* fail to establish a *prima facie* case of obviousness for the claimed invention. For example, the Office Action has failed to establish that the concentrations of 2-hydroxypropyl-beta-cyclodextrin, mannitol, EDTA, acetate buffer and/or bacteriostatic agents were recognized as result-effective variables. Furthermore, the combination of Shirley *et al.* and Dorin *et al.* also fail to teach each of the limitations of the claimed invention (*e.g.*, a composition wherein HPBCD is present at about a 500-fold to about a 700-fold molar excess with respect to interferons present within the composition). While Chen *et al.* may teach that one can add methionine and/or benzyl alcohols to a composition containing an interferon, this reference fails to remedy any of the defects noted above with respect to the combined teachings of Shirley *et al.* and Dorin *et al.* Thus, Applicant respectfully submits that a *prima facie* case of obviousness for claims 12, 20, 23, 24, 32-35 and 37 has not been established by the combination of Shirley *et al.*, Dorin *et al.* and Chen *et al.*

Furthermore, Applicant respectfully submits that the Office Action fails to establish that one skilled in the art would have been motivated to add a third anti-oxidant to the composition arising from the combination of Shirley *et al.* and Dorin *et al.* As noted in the Office Action, Shirley *et al.* add EDTA as an anti-oxidant for stabilizing IFN compositions. Dorin *et al.* indicate that protectants, such as HPBCD, are also added to reduce changes, such as oxidation. Finally, Chen *et al.* indicate that one can add methionine to a composition in order to reduce the oxidation of the interferon contained within the formulation. However, the Office Action fails to provide any reasoned statement as to why one of ordinary skill in the art would have been motivated to add a third anti-

oxidant to the composition formed by the combination of Shirley *et al.* and Dorin *et al.* As noted by the Supreme Court, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)).

A similar situation was addressed by the Board of Patent Appeals and Interferences in *Ex parte Joachim Bunger* (Appeal 2007-2803, decided July 12, 2007, 2007 WL 2020323 (Bd.Pat.App. & Interf.)). As noted by the Board in that decision:

> Despite the Examiner's unsupported assertion that person of ordinary skill in the art would have found it obvious to add an additional counterirritant to Burger's composition, we find nothing in the combination of references relied upon to suggest the use of more than one counterirritant. Instead, we find that one reading Burger and Bell in combination would recognize that Burger's composition already includes the counterirritant vitamin A and therefore would not have been motivated to add a second counterirritant to Burger's composition. As set forth in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007),
>
> > a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

Similarly, Applicant submits that the combination of references relied upon to reject the presently claimed invention does not teach or suggest the use of more than one anti-oxidant (let alone three structurally dissimilar and unrelated anti-oxidants) within the composition containing an interferon. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claim 36 is rejected under 35 U.S.C. § 103(a) as obvious over Shirley *et al.* (U.S. Published Patent Application No. 2002/0172661) in view of Dorin *et al.* (U.S. Patent No. 5,814,485) in view of Chen *et al.* (U.S. Patent No. 6,569,420) and further in view of Tsals *et al.* (U.S. Patent No. 5,858,001). The Office Action states that Tsals *et al.* teach a cartridge-based drug delivery device that is an auto-injector comprising a cartridge that serves as a reservoir and that this device is suitable

for administration of IFN formulations, including IFN-α, -β and –γ. Applicant respectfully asserts that the claimed invention is not obvious over the cited references.

It is fundamental patent law that an obviousness rejection fails if the prior art relied on does not disclose all of the limitations of the claimed invention. *See, e.g., In re Zurko*, 258 F.3d 1379, 1385-86 (Fed. Cir. 2001). As noted in the traversal of the rejections over Shirley *et al.* and Dorin *et al.* and Shirley *et al.* in view of Dorin *et al.* and Chen *et al.*, each of those combinations fail to teach all of the limitations of the claimed invention. For example, the Office Action has failed to establish that the concentrations of 2-hydroxypropyl-beta-cyclodextrin, mannitol, EDTA, acetate buffer and/or bacteriostatic agents were recognized as result-effective variables and there is no teaching or suggestion of a composition containing HPBCD at about a 500-fold to about a 700-fold molar excess with respect to interferons present within the composition. Additionally, while Chen *et al.* may teach that one can add methionine and/or benzyl alcohols to a composition containing an interferon, there is no articulated basis for adding a second and third anti-oxidant to the composition of Shirley *et al.* Applicant submits that Tsals *et al.* fail to remedy any of these defects in the various combinations of Shirley *et al.*, Dorin *et al.* and Chen *et al.* as it is solely cited for its teaching related to cartridge based drug delivery devices. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested as a *prima facie* case of obviousness has not been established for the claimed invention.

Claims 1-25 and 32-37 provisionally rejected for obviousness-type double patenting over claims 1-33 of co-pending application 10/554,602, in view of Dorin *et al.* Claims 1-25 and 32-37 are provisionally rejected for obviousness-type double patenting over claims 32-45, 48-57, 60 and 61 of co-pending application 11/597,987, in view of Dorin *et al.* Applicant respectfully asserts that the claims, as amended herein, are not obvious over the claims of the cited applications.

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Thus, in obviousness-type double patenting rejections, the Examiner must establish, in an analysis comparable to that under 35 U.S.C. § 103, that one of ordinary skill would have considered the rejected claims obvious over the conflicting claims. *See In re Braat*, 937 F.2d 589, 592-93 (Fed. Cir. 1991). In discussing a flexible approach to the issue of obviousness, the Supreme Court

nonetheless emphasized that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, *there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)). Similarly, in obviousness-type double patenting rejections, to establish that a claimed invention is "a mere variation ... which would have been obvious to those of ordinary skill in the relevant art ... there must be some clear evidence to establish why the variation would have been obvious which can properly qualify as 'prior art.'" *In re Kaplan*, 789 F.2d 1574, 1579-80 (Fed. Cir. 1986).

In the case of both obviousness-type double patenting rejections, Applicant respectfully submits that there has been no articulated reasoning with some rational underpinning that supports a fining of obviousness-type double patenting in this matter. While the '602 application may claim a composition comprising stabilized HSA-free IFN, mannitol and methionine (as an anti-oxidant) in an acetate buffer and the '987 application claims a composition comprising IFN, lysine (as an anti-oxidant) and surfactants, such as poloxamer 188 or polysorbates, in an acetate buffer, the Patent Office fails to indicate why one skilled in the art would have been motivated to add a second anti-oxidant (such as HPBCD) to the compositions of the '987 and '602 applications. It is further noted that there is no articulated reasoning as to one skilled in the art would have been motivated to add HPBCD to a composition in the molar ratios claimed (about a 500-fold to about a 700-fold molar excess with respect to the interferon present in the composition) even though claim 16 of this application was included in the obviousness-type double patenting rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

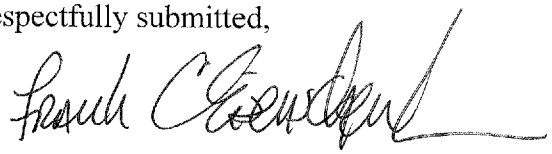
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position. Applicant expressly reserves the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/sl
Attachment: Replacement Figures 1-12